for systemic administration to a patient in combination with a coagulant in a pharmaceutically acceptable carrier for topical administration to a patient.

Please cancel claim 17.

Remarks

An Information Disclosure Statement is being forwarded under separate cover.

Informal Drawings

Formal drawings with the appropriate corrections will be submitted when there is allowable subject matter.

Rejections under 35 U.S.C. §101

Claims 1-17 have been rejected under §101 as inoperative and therefore lacking utility. This rejection is respectfully traversed.

The standard under §101 is that the claimed invention must work. While the Examiner has presented a number of reasons why the method might not work, the *in vivo* examples in the application demonstrate that the method does indeed work. See the examples at page 16-21, using pigs as the animal model. It is well known that pigs are an excellent model for human skin and that most burn and scarring studies are first done with pigs, then with humans. There are some differences, however, although these primarily relate to the areas of the snout (which were not used in applicant's studies), the hairs, and the oil glands.

Human skin is also more vascularized. See, for example, Montagna and Yun, "The Skin of the Domestic Pig", J. Invest. Derm. 43:11-22 (1964), especially discussion at page 20.

The examples clearly demonstrate that the protein C inhibitors are not inactivated before having an effect, the protein does reach the target area, and there were no adverse side effects.

Rejections under 35 U.S.C. §112, first paragraph

The specification and claims 1-17 were rejected under §112 as failing to provide an enabling disclosure and disclose the best mode known at the time the application was filed. These rejections are respectfully traversed.

Applicant has described how to use a protein C inhibitor in humans at pages 12 and 13, and at page 14 of the application. The best mode is described at page 12, lines 9-14, and page 14, lines 13-17, and 21-27, in both numerical terms and in functional terms, i.e., in an amount sufficient to saturate all the circulating protein C molecules at the time of treatment, an amount equivalent to block greater than 90% of the potential activated protein C activity in human plasma, or 1 mg HPC4 anti-protein C antibody/kg body weight. The dosage for thrombin and tissue thromboplastin is stated at page 16, lines 25-27. See also the examples at pages 17-21.

The only **legal** requirement under §112 is that applicant provide a written description of how to use the claimed invention. Applicant has, however, also provided examples of *in vivo* clinical utility in animals which are an accepted model for treatment of humans. There is no requirement for studies in humans to obtain a patent where there is an acceptable animal model. This has been repeatedly affirmed by the Board and the Court of Appeals for the Federal Circuit. Ex parte Forman does not control in this case.

Enclosed are copies of publications that demonstrate the equivalence of inhibition of protein S and protein C in facilitating coagulation: Taylor, et al., Blood 78:357-363 (1991) and J. Trauma (Suppl.) 30:197-203 (1990), which demonstrate that inhibition of protein S by C4bp binding protein or by monoclonal antibodies resulted in microvascular thrombosis, infarction and hemorrhage of the kidney when combined with an inflammatory challenge of live *E. coli* (10% of the lethal does). Neither the C4bp binding protein nor the sublethal *E. coli* alone caused microvascular coagulation, disseminated intravascular coagulation, or organ damage. Earlier work, Taylor et al., J. Clin. Invest. 79:918-925 (1987) demonstrated that inhibition of protein C activation generated a similar response in exactly the same model, when protein C activation was blocked with the monoclonal antibody to protein C, HPC4. There is similar

evidence with respect to the other claimed compounds, all of which are well characterized as to their ability to inhibit protein C. See, for example, the many publications cited at pages 7 to 11 of the application, copies of which are being submitted under separate cover with the Information Disclosure Statement.

The specification has been amended to refer to the issued patent directed to the HPC4 antibody. It is not necessary for applicant to provide any additional information or statements with respect to this antibody (of which he is not an inventor nor the owner) since the antibody must be available to the public if a U.S. Patent has issued with claims directed to the antibody, as the Examiner is of course aware.

With respect to the issue of the claims being limited to microvascular bleeding, applicant is in agreement that this is the sole type of condition which he has discovered can be treated using the disclosed methodology. Skin graft removal, however, is but one of a number of complications which can be treated, as described in the application at page 14, including burn wounds or in liver, splenic, or brain trauma, where there is microvascular damage resulting in bleeding.

In summary, applicant is entitled to claims which are not limited to pigs, since pigs are an acceptable animal model for animals other than pigs and humans; not limited to skin graft

removal since the treatment is equally useful in treatment of conditions involving microvascular injury, for which skin graft removal is a standard model; and not limited to treatment with anti-protein C antibody since it is well known to those skilled in the art of blood coagulation that there are other equivalent methods for inhibiting blood coagulation via protein C.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1 and 14 have been rejected as indefinite for inclusion of the terms "natural anticoagulant" and "tissue factor inhibition pathway". Claim 5 has been rejected as lacking antecedent basis in claim 1. Claims 6 and 9 have been rejected as dependent on inappropriate claims. Claim 17 has been rejected as duplicative of claim 16. These rejections are respectfully traversed as applied to the amended claims. Claims 10 and 17 have been cancelled as duplicative.

The term "natural" has been deleted. The term "tissue factor inhibition pathway" is well known to those skilled in the art, as demonstrated by the enclosed publication by Broze, "The Role of Tissue Factor Pathway Inhibitor in a Revised Coagulation Cascade" Seminars in Hematology 29, 3: 159-169 (1992). Antecedent basis for claim 1 has been added to claim 5.

It is not apparent what the problem with claims 6 and 9 are since they appear to be properly dependent on claims 5 and 8, respectively.

Rejections under 35 U.S.C. §102 and §103

Claims 1-4, 7, 10, and 15 have been rejected under 35 U.S.C. §102(e) as disclosed by U.S. Patent No. 5,147,638 to Esmon, et al. Claims 5, 6, 8, 9, 11-13, 14, 16, and 17 have been rejected under §103 as obvious over Esmon, et al., in combination with Suzuki, et al., Thrombosis Research 53, 271-277 (1989). These rejections are respectfully traversed as applied to the amended claims.

The present invention is the discovery that an inhibitor of natural anticoagulants such as protein C can be used to stop microvascular bleeding **in normal tissues**. The claims have been amended to reflect this.

Esmon, et al., discloses the treatment of **tumors** by the systemic administration of a compound blocking the protein C pathway. It is very clear from Esmon, et al., that the administration of the protein C inhibitor **does not have any observable effect on normal tissues**. This is directly opposite to the present situation where the treatment is to stop bleeding in normal tissues, not in tumors. There is no disclosure of combining a topical treatment with a systemic treatment since such a treatment would not be effective in killing tumors.

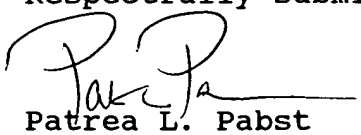
Moreover, even in the case of the tumors, these are not bleeding, as in the present situation. Accordingly, the mechanisms must be different and one would not be extrapolatable to the other.

Suzuki, et al., describes the use of topical thrombin to stop bleeding. However, there is nothing that would lead one to combine a topical treatment with a systemic treatment utilizing an inhibitor of a naturally occurring anticoagulant, **in addition to the topical treatment.**

In summary, the prior art neither discloses nor makes obvious the claimed invention: either a method for treating systemically a patient who has microvascular bleeding by systemically administering an inhibitor of a specific natural anticoagulant alone or in combination with topical administration of thrombin or tissue factor, nor such a composition.

Allowance of claims 1-9 and 11-16, as amended, is respectfully requested in view of the accompanying publications.

Respectfully submitted,



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AMENDMENT

CERTIFICATE OF MAILING UNDER 37 CFR §1.8a

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Angela Rossi

Date: August 2, 1993

Angela Rossi